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Filed : May 1, 2002

### REMARKS

Applicants thank the Examiner for the review of the instant application. Claims 1-5 are presented for examination. Applicants respond below to the specific rejections raised by the Examiner in the pending Office Action. For the reasons set forth below, Applicants respectfully traverse.

#### **Rejection Under 35 U.S.C. §101 – Utility**

The Examiner maintains his rejection of Claims 1-5 under 35 U.S.C. § 101 as lacking a specific and substantial asserted utility or a well established utility for the reasons of record.

For the reasons set forth below, Applicants respectfully disagree. Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants address each of the Examiner's arguments in turn as presented in the pending Office Action.

#### **The PTO has Concluded that the data in Example 18 are Sufficient to Establish the Utility of the Claimed Invention**

Applicants previously noted that in other applications filed by Applicants that rely on data from the exact same disclosure, Example 18, and in which the Applicants have submitted substantially the same references in support of their asserted utility, the PTO has concluded that:

Based on the totality of evidence of record, **one of skill in the art would find it more likely than not that an increase in message as measured by RTPCR would be predictive of an increase in protein expression levels**, absent evidence to the contrary. Therefore, the data presented in Example 18, which demonstrates differential expression of nucleic acids encoding PRO1180, also supports a conclusion of differential expression of PRO1180 polypeptide. Therefore, one of ordinary skill in the art would be able to use the PRO1180 polypeptide diagnostically for distinguishing normal kidney and rectal tumor tissues compared to kidney tumor and normal rectal tissue, as asserted by Applicant. *Examiner's Reasons for Allowance, Application No. 10/063,529* (emphasis added).

See also *Examiners Reasons for Allowance* in Application No. 10/063,530, No. 10/063,524, No. 10/063,582, and No. 10/063,583, all of which conclude that the data presented in Example 18,

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which demonstrate differential expression of the nucleic acids encoding certain PRO polypeptides, also support a conclusion of differential expression of the PRO polypeptides, making the claimed PRO polypeptides and antibodies that bind the PRO polypeptides useful for diagnostic purposes.

In response to Applicants' request that the Examiner recognize the utility of the claimed invention, supported by the data presented in Example 18 and the numerous cited references, as was done in the other applications referenced above, the Examiner responds by summarily stating: "Suffice it to say that each case must be decided on its own merits based on the evidence of record." *Office Action* at 3.

Applicants note that the Patent Office's conclusion that "one of skill in the art would find it more likely than not that an increase in message as measured by RTPCR would be predictive of an increase in protein expression levels," is not dependent on the particular molecule being claimed, but instead represents a conclusion regarding the state of the art based on the record. Therefore, it does not suffice to say that each case must be decided on its own merits based on the evidence of record without offering an explanation of how the record is materially different such that a different outcome is warranted.

#### Duty of the Examiner in Examination of an Application

Applicants respectfully remind the Examiner that he has a duty to consider and respond to Applicants' arguments in an attempt to clarify the issues in dispute:

The examiner should never lose sight of the fact that in every case the applicant is entitled to a full and fair hearing, and that a clear issue between applicant and examiner should be developed, if possible, before appeal. *M.P.E.P. §706.07* (emphasis added).

Applicants have attempted to respond to each of the Examiner's previous arguments, pointing out what the Applicants view as the factual errors or flaws in the Examiner's reasoning. Applicants respectfully request that the Examiner respond to Applicants' arguments in an attempt to clarify the issues in dispute prior to appeal.

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Hu et al. and LaBaer References

In response to Applicants arguments that Hu's and LaBaer's statements regarding microarray data are not relevant to the pooled sample RT-PCR data of the instant application, the Examiner states:

Applicants' arguments have been fully considered but they are not persuasive. From the evidence provided it cannot be ascertained if Kuo's RT-PCR data was [sic] consistent or inconsistent with Kuo's microarray data. Therefore, Kuo does not provide a basis for applicants asserting that applicants' PCR data are more accurate and reliable than microarray technique commented on by Hu and LaBaer. ... Hu and LaBaer caution researchers from drawing conclusions based on small changes in transcript expression. A gene whose change in expression is unrelated to the disease cannot be used as a marker for the disease no matter how accurately the change is measured. *Office Action* at 5.

This response does not address Applicants' arguments regarding Hu and LaBaer. Presumably, by "the evidence provided," the Examiner is referring to Kuo, since LaBaer doesn't provide any evidence to support his opinions. Applicants have not asserted that Kuo's microarray data is consistent or inconsistent with Kou's PCR data. Whether it is consistent or inconsistent is irrelevant to Applicants' argument, which is that those of skill in the art recognize that data generated by RT-PCR is more reliable, sensitive and accurate than microarray data. Kuo supports this assertion by stating in comparison to microarrays: "Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction..." One does not need to know if Kuo's RT-PCR data was consistent with Kuo's microarray data to rely on this statement any more than one needs to know what data LaBaer is relying on for the statement quoted by the Examiner – the Examiner cannot rely on the unsupported opinion of LaBaer, and then reject Kuo's statement because it allegedly lacks support.

The Examiner's statement that "Kuo does not provide a basis for applicants asserting that applicants' PCR data are more accurate and reliable than microarray technique commented on by Hu and LaBaer," completely ignores the teaching of Kuo which states that PCR is "more reliable and sensitive" than microarray techniques. The Examiner's statement also points out that the Examiner is relying on a completely unsupported opinion of LaBaer, who does not cite any references or data to support his assertion that many results are "disease-independent." To the extent that Hu and LaBaer "caution researchers from drawing conclusions based on small

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changes in transcript expression” because they are disease-independent, any such statement is in reference to microarray data, and is completely unsupported.

However, Kuo is not cited to provide a basis for doubting Hu and LaBaer’s statements. While Applicants do question the truth of Hu and LaBaer’s unsupported opinions, the accuracy of their statements is of no relevance because they are discussing microarray data, not pooled sample RT-PCR data as in the instant application. Therefore, Hu and LaBaer’s statements cannot support a rejection of Applicants’ pooled sample RT-PCR data. The Examiner must explain how opinions regarding microarray data, even if true, are applicable to pooled sample RT-PCR data, given Applicants’ assertions and supporting evidence that one of skill in the art would recognize RT-PCR as more reliable, sensitive and accurate. Until the Examiner provides evidence that transcript changes detected by PCR analysis of pooled normal and tumor samples are often “attributable to disease-independent differences between the samples,” the Examiner’s rejection of the data in Example 18 based on Hu and LaBaer is unsupported and without merit.

#### First Grimaldi Declaration

Applicants previously stated that they do not know how to respond to the Examiner’s statement that the first Grimaldi declaration is “in contrast with the specification’s teachings,” (see previous *Office Action* at 3), and requested that the Examiner clarify his statement.

In response to Applicants’ reasonable request for clarification, the Examiner states:

Applicants’ arguments have been fully considered but they are not persuasive. The first Grimaldi declaration states that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissue. The specification teaches that “one or more tumor tissues” were used (page 140, paragraph 0350).” *Office Action* at 7.

This is not responsive to Applicants’ request for clarification since the Examiner has not explained how the declaration is in contrast with the quoted portion of the specification or what relevance any contrast between the two statements has to Applicants’ asserted utility. The specification states: “Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject.” *Specification* at ¶[0530] (emphasis added). Applicants fail to see how this is in contrast to statements that pooled samples of tumor tissue

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and pooled samples of corresponding normal tissue were used – this statement does not preclude the use of pooled samples. It is incumbent upon the Examiner to explain how these statements are “in contrast” and what the relevance of the “contrast” is to Applicants’ asserted utility so that Applicants can address this issue on appeal.

Applicants previously stated that the Examiner’s statement that “Hu and LaBaer are evidence that a skilled artisan would consider the precise level of PRO874 gene expression as relevant” is not supported by any reasoning or citation to Hu and LaBaer, and that Hu and LaBaer teach nothing at all regarding developing diagnostic markers of cancer.

In response, the Examiner states:

Applicants’ arguments have been fully considered but they are not persuasive. Applicants previously argued that the “precise levels of gene expression are irrelevant” (Grimaldi declaration, Exhibit 1, 12/1 012004, paragraph 7). The examiner considers Hu and LaBaer as evidence that a skilled artisan would consider the precise levels of gene expression as relevant. *Office Action* at 7-8.

This argument is not responsive. First, Hu and LaBaer teach nothing at all regarding developing diagnostic markers of cancer. Second, Hu and LaBaer do not discuss the precise level of mRNA expression, but instead discuss relative differences such as 2-fold, 5-fold or 10-fold. *See Hu* at Abstract; *LaBaer* at 976. Rather than supporting the Examiner’s arguments, Hu and LaBaer support Grimaldi’s statement that “[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue.” Therefore, the Examiner has yet to explain how Hu and LaBaer support his assertion that the precise level of gene expression is required, rather than the relative difference between tumor and normal tissue as asserted by Grimaldi. Applicants request that the Examiner clarify his position to simplify the issues on appeal.

*Haynes et al. and Gygi et al. References*

Applicants have offered several arguments and illustrations to demonstrate why references such as Haynes *et al.* and Gygi *et al.* that rely on a global ratio common between all steady state mRNA levels and all steady state protein levels are not relevant to Applicants’ assertions regarding changes in mRNA level for a particular gene leading to changes in the level of the encoded protein. In response to Applicants’ arguments, including an illustration based on an analogy to gas mileage, Examiner responds by arguing:

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Applicants' arguments have been fully considered but they are not persuasive. Applicants' are assuming a change in PRO874 polypeptide expression in two different cell samples without knowing the correlation between the change, if any, in PRO874 mRNA expression and the assumed change in PRO874 polypeptide expression. ... Just as one could not predict the distances traveled on a gallon of gas in two different cars without knowing the mpg in each car, one could not predict a change in protein expression in two different cell samples without knowing that the change in mRNA is associated with a corresponding change in the level of protein. ... According to the first and second Polakis declarations, your PRO polypeptide miles per gallon of gallon of PRO mRNA gas may vary in tumor cells and normal cells. The fact that a change in mRNA level for a particular gene may typically lead to a corresponding change in the encoded protein level does not tell a skilled artisan if, or how, PRO874 polypeptide expression changes because applicants have not provided any data regarding PRO874 polypeptide expression, because there are examples where such a correlation does not exist, because applicants have not established if the present case is one in which there is such a correlation, and because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis. *Office Action* at 10 (emphasis added).

These arguments do not address Applicants' assertion that references like Haynes and Gygi are irrelevant because they rely on the premise that there a global ratio common between all steady state mRNA levels and all steady state protein levels. Whether such a ratio exists does not matter to Applicants' assertions regarding changes in mRNA leading to changes in protein level. None of the Examiner's arguments are directed to the distinction between references like Haynes and Gygi, and the references cited by Applicants to support Applicants' assertions regarding differential mRNA expression. Instead, the Examiner's arguments attack Applicants' assertions that a general correlation between changes in mRNA and protein exist, and that one of skill in the art would rely on such correlation. These arguments do not address Applicants' arguments that Haynes and Gygi are irrelevant.

Applicants invite the Examiner to either acknowledge that references like Haynes and Gygi which are premised on a global ratio of mRNA to protein are irrelevant, including their conclusions that direct measurement of protein levels is required, and withdraw his reliance on these references, or explain how such references are relevant to Applicants' assertions regarding differential mRNA expression leading to differential protein expression. Doing so would clarify the issues in dispute for appeal.

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Applicants' have previously responded to the substance of Examiner's arguments articulated above. Essentially, the Examiner's entire argument can be summarized thus:

The fact that a change in mRNA level for a particular gene may typically lead to a corresponding change in the encoded protein level does not tell a skilled artisan if, or how, PRO874 polypeptide expression changes because applicants have not provided any data regarding PRO874 polypeptide expression, because there are examples where such a correlation does not exist, because applicants have not established if the present case is one in which there is such a correlation, and because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis.  
*Office Action* at 10 (emphasis added)

Applicants have presented overwhelming evidence that changes in mRNA generally lead to changes in the corresponding level of the encoded protein, including the declarations of three experts in the field, and over 100 references which directly or indirectly support this position.

Were the Examiner to acknowledge that based on the record, Applicants have established that there is such a general rule or correlation, rather than stating that there "may be," the remaining issue regarding the Examiner's argument above would be whether the Applicants can rely on a general rule with admitted exceptions to provide utility, or if Applicants must provide specific evidence of the PRO874 polypeptide expression. The Examiner apparently believes that if there is any exception to a correlation relied on for utility, a doubt is raised regarding the utility since it is not known if the claimed molecule follows the rule or the exception, and therefore specific direct evidence of utility is required. Applicants assert that a correct reading of the utility standard articulated by the Courts and the PTO indicate that the correlation need to be absolute or exact, but only reasonably indicative of the asserted utility. *See Nelson v. Bowler*, 626 F.2d 853, 856-57; *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051; *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564. Applicants could then appeal this issue to the Board of Patent Appeals and Interferences for clarification.

Therefore, in an attempt to clarify the issues in dispute, Applicants request that the Examiner acknowledge that based on a careful consideration of the *entire record*, Applicants have established by a preponderance of the evidence (*i.e.* more likely than not) that those of skill in the art recognize that changes in mRNA level for a particular gene generally, but not always, lead to a change in the level of the encoded protein. Doing so would simplify issues for appeal.

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Allman et al. Reference

Applicants have argued that the Allman et al. reference is not contrary to Applicants' assertion that, generally, a change in mRNA expression levels leads to a change in the encoded protein expression level. The Examiner has responded by arguing:

Applicants' arguments have been fully considered but they are not persuasive. ... To be consistent applicants must also accept the argument that no change in BCL-6 mRNA levels would lead to no change in the levels of BCL-6 protein, or that a change in BCL-6 protein expression would be associated with a change in BCL-6 mRNA expression. Allman demonstrates that this is not so. Therefore, Allman does not support applicant's position. *Office Action* at 11 (emphasis added).

This response does not address Applicants' argument as the Examiner continues to conflate cause and effect. It is not inconsistent for the Applicant to assert that changes in mRNA expression generally lead to changes in protein level, and at the same time acknowledge that not all changes in protein level are a result of changes in mRNA. Because not all changes in protein level are a result of changes in mRNA, one cannot assume that no change in BCL-6 mRNA ensures no change in BCL-6 protein, or that a change in BCL-6 protein is associated with a change in BCL-6 mRNA.

As an analogy, consider the assertion that increasing the number of home runs during a game increases a baseball team's score. It is not inconsistent to state that when no one is hitting home runs, you cannot assume that the team's score isn't increasing because there are other ways to increase the score (e.g. a bases loaded single). Similarly, it is not inconsistent to state that if a team's score increases, it does not necessarily mean that someone hit a home run. Scoring runs does not result in, or necessarily reflect, home run hitting, but home run hitting does cause scoring. Home run hitting is the cause, scoring is the effect. Similarly, increasing protein levels does not cause, or necessarily reflect increased mRNA, but increased mRNA does generally cause increased protein. A change in mRNA level is the cause, a change in protein level is the effect. Applicants respectfully request that the Examiner acknowledge that his arguments based on Allman are conflating cause and effect, and that Allman is not contrary to Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the encoded protein level. Doing so would simplify issues for appeal.

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Chen et al. Reference

Applicants have argued that portions of Chen et al. that, like Hayes and Gygi, examined global relationships between mRNA and protein are not relevant. The Examiner has responded by arguing:

Applicants' arguments have been fully considered but they are not persuasive. Applicants' rely on the statement in Chen that "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (sentence bridging pages 311-312).

However, this global analysis of the relationship between mRNA and protein abundance was in addition to and distinct from Chen's correlation a mRNA/protein abundance in the tumor samples, and the examiner did not rely on this global analysis. *Office Action* at 12 (emphasis added).

Applicants thank the Examiner for stating on the record that he is not relying on this portion of the Chen reference. Applicants respectfully request that the Examiner also state for the record that he is no longer relying the Haynes and Gygi references which conducted the same kind of study.

In addition to the study examining a global correlation between mRNA and protein, Chen et al. report that they examined a correlation between mRNA level and protein level for individual genes by plotting the mRNA vs. protein for numerous samples (a mixture of tumor and non-tumor samples). Applicants have argued that because Chen et al. did not attempt to examine genes where there was a change in mRNA expression level, it is not known if the genes examined had substantial changes in mRNA across the samples tested. As a result, Chen's conclusions regarding a lack of correlation between mRNA and protein levels is not contrary to Applicants' assertion that generally speaking, a change in mRNA level leads to a corresponding change in protein level. The Examiner has responded by arguing:

Applicants' arguments have been fully considered but they are not persuasive. ... According to applicants exhibits, arguments, declarations, and asserted dogma changes in the level of an mRNA are associated with a corresponding change in the level of the encoded polypeptide. Therefore, according to applicants' exhibits, arguments, declarations, and asserted dogma, a change in the level of an mRNA should be correlated with a corresponding change in the level of the encoded protein regardless of the type of sample. However, Chen states:

"Correlation analyses showed that protein abundance is likely a reflection of the transcription for a subset of proteins, but translation and post-translational modifications also appear to

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influence the expression levels of many individual proteins in lung adenocarcinomas.” Paragraph bridging pages 304 and 306.

Applicants have not tested PRO874 polypeptide expression. It is unknown if the reported change in PRO874 mRNA expression is associated with a corresponding change in PRO874 polypeptide expression. *Office Action* at 12 (emphasis added).

This argument is not responsive to Applicants’ arguments. As the underlined portion of the Examiner’s statement above indicates, Applicants’ assertions are with regard to differential mRNA expression. As Applicants have previously noted, it is unknown if Chen et al. examined differentially expressed mRNA, and therefore their finding of a lack of correlation is not contrary to Applicants’ assertions. The statement from Chen quoted by the Examiner is not contrary to Applicants’ asserted utility, since it in no way contradicts Applicants’ assertion that differential mRNA expression generally result in a corresponding differential expression of the encoded protein. Applicants respectfully request that the Examiner respond to Applicants’ arguments regarding Chen et al. In particular, Applicants request that the Examiner address Applicants’ arguments that because it is not known if Chen examined differentially expressed genes, the reported lack of correlation is not relevant to Applicants’ assertions. If the Examiner disagrees, Applicants invite the Examiner to state on the record why Applicants’ arguments are wrong, and not simply state that they are “not persuasive.”

#### Hancock Reference

Applicants have argued that Hancock’s statement that “the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling” is not contrary to Applicants’ assertions. The Examiner has responded by arguing:

Applicants’ arguments have been fully considered but they are not persuasive. Hancock is evidence that a situation, such as the present one, wherein only a change in transcripts is presented, is a situation that would require or constitute carrying out further research to identify or reasonably confirm a “real world” context of use for the polypeptide because applicants have not provided any testing of PRO874 polypeptide expression. The specification lacks a sufficient correlation between the test performed on PRO874 mRNA expression and the asserted utility of the claimed polypeptides. *Office Action* at 13.

This is unresponsive to Applicants’ arguments. If Hancock is basing his statement that “the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling” on data where protein levels change, but mRNA levels do not change, his statement is not relevant to Applicants’ assertions. Therefore, as Applicants have

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previously argued, Hancock is not evidence that is contrary to Applicants' assertion. Applicants respectfully request that the Examiner respond to Applicants' arguments regarding Hancock, and explain how Hancock is "evidence that a situation, such as the present one... is a situation that would require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use for the polypeptide."

The Declarations of Dr. Polakis

Applicants have submitted a second declaration of Dr. Polakis, including data for evaluation by the Examiner. In response, the Examiner argues:

Applicants' arguments have been fully considered but they are not persuasive. The second Polakis declaration has been considered. Like the first Polakis declaration, the second Polakis declaration does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. ... The facts to be established are whether or not the disclosed change in PRO874 transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO874 transcripts and a corresponding change in PRO874 polypeptides levels. The declarations do not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue.

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Both the first and second Polakis declarations indicate that the data was generated using microarray analysis, which applicants' have disparaged as inaccurate and unreliable. ... Even if the examiner were to accept Dr. Polakis' conclusion, it still would be considered evidence that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer because 20% of the cases examined do not show a correlation, according to first Polakis declaration, and 10% of the cases examined do not show a correlation according to second Polakis declaration. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to the Polakis declarations. *Office Action* at 14-16 (emphasis added).

Applicants emphasize that they have not "disparaged as inaccurate" microarray data. Applicants have merely argued that conclusions regarding "disease-independent" differences between samples based on microarray data cannot be extended to RT-PCR data because those of

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skill in the art recognize that the latter is more accurate, reliable, and sensitive than microarray data.

The Examiner continues to rely on his personal opinion that because there are exceptions to the general correlation, one of skill in the art would not rely on differential PRO874 mRNA expression data to predict PRO874 protein expression. The Polakis, Grimaldi, and Scott Declarations, all by experts in the field, state that the correlation is sufficiently reasonable that one of skill in the art would rely on differential mRNA expression data to predict protein expression.

Applicants offer the Scott, Grimaldi, and Polakis Declarations, not to unequivocally prove that PRO874 polypeptide is differentially expressed, but rather to prove that one of skill in the art would be more likely than not to believe that because the PRO874 mRNA as measured by RT-PCR is differentially expressed, the PRO874 polypeptide will likewise be differentially expressed. Applicants do not need to provide direct evidence of PRO874 polypeptide expression to establish the asserted utility. Indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101. *Nelson v. Bowler*, 626 F.2d 853, 856-57, *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051; *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564. In light of the proper utility standard, it is improper for the Examiner to reject the Polakis Declaration because it does not provide direct evidence of differential PRO874 polypeptide expression – that is not what the Polakis Declaration is required to do. Instead, the Polakis Declaration is evidence that Applicants' evidence of utility is sufficient to convince one of skill in the art that the asserted utility is more likely than not true.

Applicants request that the Examiner acknowledge that there are cases where direct evidence of utility is not required because there is a reasonable correlation between the asserted utility and the evidence provided. In such cases, declarations establishing the reasonableness of the correlation between the asserted utility and the evidence provided, as well as reliance thereon, are probative. While the Examiner may not agree that this is one of those cases, such an acknowledgement would place the Polakis Declaration in the proper perspective – evidence that one of skill in the art would rely on differential mRNA data to predict protein expression – rather than viewing it as insufficient because it does not contain direct evidence of PRO874 polypeptide expression.

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The Declaration of Dr. Scott

To support their assertion that a change in mRNA level generally leads to a corresponding change in the encoded protein level, and that one of skill in the art would rely on mRNA measures to predict protein levels, Applicants previously submitted the declaration of Dr. Randy Scott. The Examiner responds by arguing:

The declaration under 37 CFR 1.132 filed by Randy Scott is insufficient to overcome the rejection of claims 1-5. Dr. Scott bases his conclusions on microarray data, which applicants have disparaged as lacking sensitivity, inaccurate and unreliable. Further, Dr. Scott does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in any type of tissue sample. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, ... Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO874 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO874 polypeptide, the specification does not provide some immediate benefit to the public for the PRO874 polypeptide. *Office Action* at 16 (emphasis added).

Applicants again emphasize that they have not “disparaged” microarray data “as lacking sensitivity, inaccurate and unreliable.” Applicants have merely argued that conclusions regarding “disease-independent” differences between samples based on microarray data cannot be extended to RT-PCR data because those of skill in the art recognize that the latter is more accurate, reliable, and sensitive than microarray data.

As to the remainder of the Examiner’s argument – that because there are exceptions to the relationship between changes in mRNA and changes in protein, Applicants must provide actual testing of PRO874 polypeptide – Applicants note that the Scott Declaration states exactly the opposite. Dr. Scott, an independent expert in the field of molecular diagnostics, states:

[I]t has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified ... without the need to directly measure individual protein expression levels. *Scott Declaration* at ¶10 (emphasis added).

Dr. Scott’s declaration directly contradicts the personal opinion of the Examiner, and the Examiner has not given any reason to reject the Scott Declaration, other than the inaccurate

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statement that Applicants have disparaged microarray data. Without basis, the Examiner is ignoring the declaration of an independent expert in the field who states that one of skill in the art would rely on a correlation between changes in mRNA to predict changes in protein, in spite of the exceptions to the general correlation, without directly measuring the individual protein expression.

The Examiner has not explained his basis for rejecting Dr. Scott's opinion – he merely repeats the arguments made before the Scott Declaration was submitted. Applicants remind the Examiner that case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew. *See in re Rinehart*, 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976); *In re Piasecki*, 745 F.2d 1015, 226 USPQ 881 (Fed. Cir. 1985). As the Examiner has previously stated, when considering the weight to be given an expert opinion, the Examiner should evaluate, among other things:

- (1) The nature of the fact sought to be established.
- (2) The strength of any opposing evidence.
- (3) The interest of the expert in the outcome of the case.
- (4) The presence or absence of factual support for the expert's opinion.

(1) The nature of the fact sought to be established: The nature of the fact to be established is whether one of skill in the art would believe that differential mRNA levels reflect differential protein levels, such that they would rely on this general correlation to predict changes in protein by measuring changes in mRNA without directly measuring the individual protein expression. The nature of this question is such that it is best answered by those who are actually practicing scientists in the field of molecular and cancer biology, like Dr. Scott.

(2) The strength of any opposing evidence: The Examiner has not submitted any opposing evidence. The Examiner continues merely to rely on a few references which he asserts establish that there are exceptions to the general correlation between changes in mRNA and changes in protein. Although Applicants dispute the relevance of the Examiner's evidence, they have acknowledged that exceptions exist. However, the fact sought to be established is not whether exceptions to the rule exist, but rather, whether the correlation between Applicants' evidence of utility and the asserted utility is well-established enough that one of skill in the art would accept Applicants' asserted utility based on the PRO874 RT-PCR mRNA data. The Examiner has not presented any evidence that those of skill in the art would not rely on differential RT-PCR mRNA data to predict protein expression for diagnostic utility.

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(3) The interest of the expert in the outcome of the case: Dr. Scott is an independent expert in the field. He is not an employee of the Assignee, nor is he an inventor of the instant application.

(4) The presence or absence of factual support for the expert's opinion: Dr. Scott relies on his extensive experience in the field, as well as the fact that an entire industry has developed around technology to assess differential mRNA expression. As stated previously, there would be little reason to study changes in mRNA expression levels if those changes did not result in corresponding changes in the encoded protein levels. In addition, Dr. Scott's conclusions are supported by the declarations of two other experts in the field, and over 100 other supporting references which Applicants have submitted.

When the factors outlined above are considered as a whole, it is clear that the Scott Declaration cannot simply be summarily dismissed. Applicants respectfully request that the Examiner properly consider the Scott Declaration, and articulate a proper basis for rejecting Dr. Scott's independent expert opinion – merely repeating the Examiner's personal opinion that one of skill in the art would require actual testing of the molecule is not a sufficient basis to reject the opinion of an expert in the field to the contrary, especially given the other evidence of record (3 expert declarations and over 100 references) which support Dr. Scott's conclusions.

*The Examiner's Position is Inconsistent with the Utility Guidelines and the Courts*

In response to Applicants' evidence and arguments, the Examiner takes the position that Applicants must present specific evidence directly demonstrating the utility of the claimed antibodies – specifically, direct evidence of differential expression of PRO874 polypeptide in tumor and normal tissue. Applicants submit that this requirement is inconsistent with the Utility Guidelines and the courts.

In response to Applicants, the Examiner makes the following arguments:

Applicants' arguments have been fully considered but they are not persuasive. It is the examiner's position that applicants should provide substantial evidence of a diagnostic utility unless one of skill in art would accept such utility as obviously correct. There is no indication that a skilled artisan would accept without question that the reported change in PRO874 transcripts is tumor-dependent or that the PRO874 polypeptide is differentially expressed in tumor tissue as compared to normal tissue in a manner consistent with the reported change in PRO874 transcripts. Neither the specification nor any of Applicants' arguments, exhibits, declarations or other evidence provide any specific data disclosing if or

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how PRO874 polypeptide expression changes in tumor tissue. Instead, Applicants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO874 transcripts and PRO874 polypeptide expression to argue that it is more likely than not that a change in PRO874 transcripts is correlated with an assumed change in PRO874 polypeptide expression. Without any evidence of the expression of PRO874 in tumor tissue this argument is of no avail to Applicants. Applicants' arguments, exhibits and declarations only show that it is not implausible that invention will work for its intended purpose. In view of the countervailing evidence, Applicants' arguments, exhibits and declarations are insufficient to meet the utility requirement because they are insubstantial evidence that expression of the PRO874 polypeptide changes in a manner that corresponds to the reported change in PRO874 transcripts. *Office Action* at 18-19 (emphasis added).

The Examiner's analysis is flawed. Were the Examiner's analysis correct, the Courts in *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. 881 (C.C.P.A. 1980), *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985), and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) would have reached a different conclusion. In those cases, there were exceptions to the correlations relied on for the asserted utility. In addition, the correlation was not specific to the claimed molecule, but was a general correlation applicable to the class of compounds being tested. According to the Examiner's analysis, because the in vitro screens and preliminary tests in those cases did not always correlate with the asserted utility, and were not specific to the molecule tested, one of skill in the art would have a reason to doubt the asserted utility, and actual direct proof of the asserted utility would be required.

The Examiner's position was rejected by the courts – the courts did not require direct proof of the asserted utility even where there was evidence of exceptions to the general correlation relied on by the applicants: "Of course, it is possible that some compounds active *in vitro* may not be active *in vivo*. But, as our predecessor court in *Nelson* explained, a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices." *Fujikawa*, 93 F.3d at 1565 (emphasis added).

Contrary to the Examiner's assertion that "[t]here is no indication that a skilled artisan would accept without question that ... the PRO874 polypeptide is differentially expressed in tumor tissue as compared to normal tissue in a manner consistent with the reported change in PRO874 transcripts," Applicants have provided the declarations of three experts in the field, and over 100 supporting references. This evidence establishes that one of skill in the art would be

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reasonably convinced that the PRO874 polypeptide will exhibit the asserted diagnostic utility, and case law establishes that this is sufficient. Thus, the Examiner's position is untenable in light of the evidence of record and relevant case law – exceptions to the correlation relied on for utility does not result in a requirement for direct evidence of the asserted utility.

Applicants' respectfully request that the Examiner reexamine his contention that only direct evidence of PRO874 polypeptide expression can provide the required evidence of utility:

Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965) ... Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* 2107.02 VII (emphasis in original).

### **Conclusion**

Applicants have established that it is more likely than not that one of skill in the art would believe that because the PRO874 mRNA is differentially expressed in lung tumors as compared to normal lung tissue, the PRO874 polypeptide will likewise be differentially expressed in lung tumors. Accordingly, when the proper standard for utility is applied to the evidence of record, it is clear that this differential expression of the PRO874 polypeptide establishes the claimed antibodies useful as diagnostic tools for cancer, particularly lung cancer. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the utility rejection under 35 U.S.C. §101.

### **Rejections under 35 U.S.C. § 112, first paragraph – Enablement**

The Examiner maintains his rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph. Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Thus, since the enablement rejection is based on the rejection of the claims as lacking utility, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

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**Rejections under 35 U.S.C. § 112, first paragraph – Written Description, New Matter**

The Examiner has rejected pending Claims 1-5 under 35 U.S.C. §112, first paragraph, as containing new matter. *Office Action* at 20-21. Specifically, the Examiner objects to claim limitations related to amino acids 34-321 of SEQ ID NO:10. Applicants have argued that the Examiner's previous arguments misstate the written description standard and ignore the clear teaching of the specification.

In response, the Examiner makes the following arguments relating to residue #34:

Applicants' arguments have been fully considered but they are not persuasive. The disclosure that it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides makes it clear that Applicants have not adequately described "amino acids 34-321 of SEQ ID NO: 10" because there is no evidence of record that amino acid #34 is employed as a start site.

In the absence of any evidence that amino acid #34 is employed as a start site, the generic disclosure of what may be possible or conceivable does not convey with reasonable clarity to those skilled in the art that Applicants were in possession of the invention as now claimed. *Office Action* at 21 (emphasis added)

This argument is not persuasive, as it ignores a fundamental principle of the written description requirement – all that is required to satisfy the written description requirement is that "the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." *M.P.E.P.* §2163.02 (internal citations omitted, emphasis added).

Applicants have indicated in the specification that that "other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides." The instant case is similar to a generic chemical structure with a variable "R" group that is defined in the specification. Where the genus of chemicals defined by the structure is small (e.g. 8), the fact that a genus is described does not prevent the applicant from claiming a particular species by selecting a particular "R" group – the description of the small genus and various "R" groups is sufficient.

In the instant application, there are eight methionine residues in SEQ ID NO:10. At a minimum, as the Examiner has acknowledged, there is generic written description support for the "genus" of proteins starting at any one of these methionine residues. This "genus" contains eight

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immediately identifiable species since SEQ ID NO:10 is disclosed, and one of skill in the art knows which residues are methionine. Given the "generic" description, combined with the specifics of SEQ ID NO:10, each of the eight species in the "genus" is adequately described. This is particularly true for the claimed species, since methionine #34 is the first methionine in SEQ ID NO:10. Applicants request that the Examiner clarify what is meant by, and explain his basis for requiring, "evidence of record that amino acid #34 is employed as a start site," as Applicants are not aware of any support for this test in the M.P.E.P. or the case law.

### CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 12, 2007

By: AnneMarie Kaiser  
AnneMarie Kaiser  
Registration No. 37,649  
Attorney of Record  
Customer No. 30,313  
(619) 235-8550

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030507